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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/753,169 | 01/02/2001 | Cy A. Stein | 55669-A-PCT-US/JPW/GJC | 9695 |

7590 01/05/2004

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|---|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 01/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/753,169 | STEIN ET AL. | |
| | Examiner | Art Unit | |
| | Janet L. Epps-Ford, Ph.D. | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *5,9,17-41 and 43* is/are pending in the application.

4a) Of the above claim(s) *17-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. Claims 5, 9, 17-14 and 43 are currently pending in the instant application.

2. Claims 17-41 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 20.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Response to Arguments*

### *Claim Rejections - 35 USC § 112*

4. Claim 43 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the pharmaceutical compositions of the instant invention in an *in vitro* method, does not reasonably provide enablement for using the claimed pharmaceutical compositions *in vivo* for therapeutic purposes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim, for the reasons of record set forth in the Office Action mailed 6-18-03.

Applicant's arguments filed 9-22-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that "the claimed active antisense, though they may vary in the extent they downregulate protein expression, all are active in the different cell lines regardless of delivery agent. Applicants also note that the therapeutic activity of the claimed oligonucleotides is defined by their sequence – control sequences do not work (see specification, page 22,

lines 5-6)." Furthermore, Applicants argue that different levels of inhibition does not preclude activity or usefulness. Accordingly, applicants maintained that the rejected claims comply with the provisions of 35 U.S.C. 5112, and request that the Examiner reconsider and withdraw this ground of rejection.

Contrary to Applicant's assertions, it is first noted that the instant claims do not recite any particular mRNA target for the claimed antisense oligonucleotides, nor do they recite any particular length for the claimed antisense oligonucleotides. The instant claims merely recite antisense oligonucleotides comprising nucleotide sequence A, B, C, D, E, F, G, H, I, J, K, L or M (SEQ ID NO: 1-13), respectively, wherein the oligonucleotide is conjugated to a peptide or comprises an –Ome group at their 2' position. However, Applicants have not demonstrated how to use an antisense oligonucleotide of an unknown length (for example 100 nucleotides in length), wherein said oligonucleotide is conjugated to a peptide of unknown composition, or comprising 2'-Ome modifications, for therapeutic purposes. Although, Applicants have demonstrated some *in vitro* inhibition of bcl-x, there is no evidence that these effects are correlated with any phenotypic changes in the cells that are treated with the antisense oligonucleotides 18-20 nucleotides in length. Furthermore, due to the unpredictability associated with the behavior of antisense oligonucleotides in a cellular environment, as it relates to the sequence composition, sequence length, and modifications as described in the previous Office Action, Applicant's *in vitro* observations can not be used to predict the pharmacokinetic behavior of the antisense oligonucleotide *in vivo*, or provide evidence of therapeutic utility.

As stated in the prior Office Action, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the delivery of antisense *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

(New Grounds of Rejection)

5. Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description)

Claim 43 is drawn to a pharmaceutical composition comprising an effective amount of an antisense oligonucleotide analog thereof of claim 5 or 9 and a pharmaceutically acceptable carrier, wherein the effective amount is between 0.1 μM and 10 μM. It is noted that the scope of this claim encompasses antisense oligonucleotides or analogs of unknown length and composition.

According to the specification as filed the antisense oligonucleotides of the present invention are disclosed as being functional to reduce or eliminate the expression of bcl-xL (see page 1, lines 19-20). However, the instant claims do not recite this particular functional limitation. The instant claims read on antisense oligonucleotide, i.e.

one targeting any particular gene, from any particular organism, including all polymorphic and allelic variants of the claimed sequences.

One of ordinary skill in the art would not be able to predict the structures of all nucleotide sequences encompassed by the instant claims, because they comprise a broad number of nucleotide sequences, and there is no common structure shared among the species that is related to any particular common function, i.e. to reduce or eliminate the expression of bcl-xL, such that the ordinary skilled artisan would be able to immediately envision all analogs of the sequences encompassed by the instant claims, such that said analogs are functional antisense oligonucleotides without the need for further experimentation.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing

identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Applicants have not provided the nucleotide structures of the full scope of analogs of the antisense oligonucleotides encompassed by the instant claims. It is evident that further experimentation would be required in order to identify the full scope of oligonucleotides encompassed by the claimed invention. Therefore, it is concluded that Applicants were not in possession of the full scope of the claimed antisense oligonucleotides at the time of filing of the instant application.

***Double Patenting***

6. Claims 5, 9 and 43 remain provisionally rejected under the judicially created doctrine of double patenting over claims 9, 36-50, 53-54, 58, and 61-62 of copending Application No. 09/832,648 in view of Manoharan et al. Sanghvi et al., Matteucci et al. and Arnold et al. for the reasons of record set forth in the prior Office Action mailed 6-18-03. Applicant's arguments filed 9-22-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the double patenting rejection made by the Examiner in the June 18, 2003 Office Action becomes moot because the Examiner's arguments are premised on sequences not cited in the pending claims. Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection. Applicant's response is confusing since SEQ ID NO: 4 is still recited in the current claims as amended, and in the claims of copending application 09/832,648.

(New Grounds of Rejection)

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 5, 9 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pollman et al. in view of Gibbons et al. (US Patent No. 5,776,905).

Claims 5 and 9 are drawn to antisense oligonucleotides comprising nucleotide sequence A, B, C, D, E, F, G, H, I, J, K, L or M (SEQ ID NO: 1-13), respectively, wherein the oligonucleotide is conjugated to a peptide or comprises an –Ome group at their 2' position. Claim 43 is drawn to a composition comprising an effective amount of an antisense oligonucleotide or analog thereof, and a pharmaceutically acceptable carrier, wherein the effective amount is between 0.1 μM and 10 μM.

Pollman teach inhibition of neo-intimal cell bcl-x expression comprising transfecting a solution comprising Lipofectamine and an antisense oligonucleotide directed against bcl-x into atheromatous (i.e. vascular) lesions in the rabbit carotid artery (Methods section, p. 226). Specific down regulation of the bcl-$x_L$ splice isoform resulted in regression of atheromatous lesions (see Figure 8, page 226). Additionally, Pollman et al. discloses 3 phosphorothioate modified antisense oligonucleotides, wherein antisense sequence-3 (#3; see Methods section, page 226) comprises the consecutive nucleotide sequence of SEQ ID NO: 2 of the instant application.

However, Pollman et al. does not teach antisense oligonucleotides conjugated to a peptide or wherein one or more of the oligonucleotide's sugars contain an –Ome group at their 2'-position. Additionally, Pollman et al. does not teach pharmaceutical compositions comprising an effective amount of an antisense oligonucleotide, wherein the effective amount is between 0.1 μM and 10 μM.

Additionally, Gibbons et al. teach a method for reducing the dimensions of a neointimal vascular lesion in a patient comprising localized delivery of an antisense oligonucleotide that inhibits the expression of bcl-$x_L$ (col.2 lines 28-42). Gibbons et al. teach administration of antisense oligonucleotides comprising methods known in the art for enhancing the uptake if nucleic acids by cells, for example delivery systems include Sendai virus-liposomes, cationic liposomes polymeric gels or matrices, and porous balloon catheters (col. 7, lines 45-60). Gibbons et al. teach that the antisense oligonucleotides used in the method for reducing the expression of bcl-$x_L$ in cells may comprise modifications to enhance oligonucleotide intracellular stability and binding affinity. In a specific embodiment Gibbons et al. teach that the 2'-OH ribose sugar may

be altered to form 2'-O-methyl (col. 5, lines 6-28). [It is noted that since the specification as filed does not clearly define what the term "-OMe" is intended to encompass, this term is interpreted as encompassing either "2'-O-methyl" or "2'-O-methoxy."] The oligonucleotides of Gibbons et al. can also be conjugated to poly-L-lysine (considered a peptide) or other polyamines to enhance delivery to cells (see col. 5, lines 52-56).

Moreover, Gibbons et al. teach that compounds having the desired pharmacological activity may be administered in a physiologically acceptable carrier to a host for treatment intimal lesions. Depending upon the manner of introduction, the compounds may be formulated in a variety of ways. The concentration of therapeutically active compound in the formulation may vary from about 0.1-100 wt. % (col. 7, lines 19-25).

It would have been obvious to one having ordinary skill in the art at the time the invention was made, to design the antisense oligonucleotide according to the present invention comprising a sequence according to A, B, C, D, E, F, G, H, I, J, K, L or M (SEQ ID NO: 1-13), respectively, wherein the oligonucleotide is conjugated to a peptide or comprises an –Ome group at their 2' position. One of ordinary skill in the art would have been motivated to specifically design antisense oligonucleotides comprising the sequence according to SEQ ID NO: 2 (B), since this sequence is expressly disclosed by Pollman et al. as being effective to inhibit the expression of bcl-x mRNA. Additionally, one of ordinary skill in the art would have been motivated to modify the sequence disclosed by Pollman et al. to be conjugated to a peptide or further to comprise a 2'-Ome sugar modification, since Gibbons et al. teach these modifications would enhance the cellular properties of antisense oligonucleotides targeting bcl-x.

Moreover, in regards to the claimed effective amount of antisense oligonucleotide recited in the composition of claim 43, specifically wherein the effective amount is between 0.1 μM and 10 μM. Absent evidence to the contrary, the teachings of Gibbons et al. which states that the concentration of active compounds used in the design of formulations comprising antisense oligonucleotides, may vary from about 0.1-100 wt. % (col. 7, lines 19-25), encompasses Applicants claimed range of between 0.1 μM and 10 μM.

Therefore, the invention as a whole would have been *prima facie* obvious at the time the invention was made over Pollman et al. in view of Gibbons et al.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Fri, 8:30AM-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

*JLE*
December 28, 2003